UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/503,758	02/14/2000	William G. Thilly	2909.1000-004	7123

21005 7590 08/18/2004		EXAMINER
HAMILTON, BROOK, SMITH & REYNOLDS, P.C.		STRZELECKA, TERESA E

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/503,758	THILLY, WILLIAM G.
	Examiner	Art Unit
	Teresa E Strzelecka	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2004*.

2a)☐ This action is **FINAL**.   2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,25-28,33,59,60 and 62* is/are pending in the application.

    4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,25-28,33, 59, 60, 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

    Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

    a)☐ All   b)☐ Some * c)☐ None of:

      1.☐ Certified copies of the priority documents have been received.

      2.☐ Certified copies of the priority documents have been received in Application No. _____.

      3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

    * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/12/2004*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed May 12, 2004. Claims 1-65 were

previously pending, with claims 1-22, 24, 29-32 and 34-58 withdrawn from consideration.

Applicant cancelled claims 1-22, 24, 29-32, 34-58, 61 and 63-65 and amended claims 23, 26-28, 59,

60 and 62.

2. Applicant's amendments, arguments and claim cancellations overcame the following

rejections: rejection of claims 61 and 63-65 under 35 U.S.C. 112, first paragraph; rejection of claims

23, 25-28, 33 and 59-65 under 35 U.S.C. 112, second paragraph; rejection of claims 25, 33, 59 and

60 under 35 U.S.C. 103(a) over Kervinen et al., Khrapko-1 et al., Khrapko-2 et al. All other

rejections are maintained for reasons given in the "Response to Arguments" section below.

3. This office action is made non-final because of new grounds for rejection.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on May 12, 2004 was filed after the

mailing date of the non-final office action on January 8, 2004. The submission is in compliance

with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being

considered by the examiner.

Response to Arguments

5. Applicant's arguments filed May 12, 2004 have been fully considered but they are not

persuasive.

A) Regarding the rejection of claims 23 and 62 under 35 U.S.C. 102(b) as anticipated by

Kervinen et al. as evidenced by Margaglione et al., Applicant argues that

a) The amendment to claim 23 adding a limitation of identification of point mutations in one or more samples obviates this rejection, as "Kervinen et al. only teach the identification of point mutations through a database search and not in a sample".

b) Kervinen et al. do not teach identification of point mutations in the apoE gene locus, but demonstrate determination of frequencies of previously known alleles and do not teach characterizing unknown mutations. Applicant's invention allows sampling of all inherited point mutations.

c) Kervinen et al. do not disclose that apoE polymorphisms are knock-out mutations, which are defined as mutations which inactivate the gene.

Regarding a), Kervinen et al. do teach obtaining blood samples from 87 women and 8 men (page 90, paragraphs 4-6).

Regarding b), the apoE4 allele is a point mutation, T->C subsitution at position 3745 of the apoE gene (see Paik et al., PNAS, vol. 82, pp. 3445-3449, 1985; page 3448, second paragraph). The limitations of screening for unknown mutations or screening for all inherited point mutations are not currently in the claims.

Regarding c), Applicants did not define what it means that the gene is inactive. Therefore, any point mutation in a gene, as explained in the "Claim Interpretation" section of the previous office action, is considered a knock-out mutation.

The rejection is maintained.

Claim Rejections - 35 USC § 112

6.   The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7.   Claims 25-28, 33, 59 and 60 rejected under 35 U.S.C. 112, first paragraph, as failing to

comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or

with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement

requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8

USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue
> experimentation have been summarized by the board in Ex parte Forman. They
> include (1) the quantity of experimentation necessary, (2) the amount of direction or
> guidance presented, (3) the presence or absence of working examples, (4) the nature
> of the invention, (5) the state of the prior art, (6) the relative skill of those in the art,
> (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 25-28, 33, 59 and 60 are broadly drawn to methods of identifying all inherited point

mutations occurring at a frequency at or above $5 \times 10-5$. However, as will be further discussed, there

is no support in the specification and prior art for these methods as claimed. The invention is a

class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry

and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Guidance in the Specification.

The specification provides no evidence that the claimed methods would indeed determine all

inherited point mutations in any one gene. The guidance provided by the specification amounts to

an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the

claimed invention. The specification discloses a theoretical model predicting a distribution of

mutations in a population at risk for pancreatic cancer (Example 1). On page 37, for example,

Applicant cites some experimental data on the mutations in Hprt gene and APC genes. In the Hprt

gene, frequencies of individual point mutations were found to range from 0.01% to more than 10 %

(lines 5-7), and frequencies of individual SNPs in the APC gene ranged from 1 to 40% (lines 19-

21). Applicant calculates expected frequencies of mutations based on the monogenic or polygenic

models (pages 38-40). Example 2 presents a theoretical model colon cancer mortality based on

assumptions about cancer progression, mutation rates and mutation frequencies in humans,

mortality rates, etc. Example 3 provides theoretical estimates of deleterious point mutation

frequencies, however, the foundations of these estimates are not clear. There is no guidance in the

specification about how to determine whether all of the inherited point mutations for a given gene

were determined.

Working Examples

The specification has no working examples of how to determine the frequency of all

inherited point mutations in a given gene in a population. Further, no evidence is provided of even

a single gene for which all inherited point mutations were determined. On page 141 (lines 14-28)

and page 142, for example, applicant describes determination of point mutations in short stretches

(from 66 to 121 bp) of exon 15 of the APC gene and exons 2-9 of the Hprt gene. One point

mutation was found in exon 15 of the APC gene, at a frequency of 11% (Table 7). In the Hprt gene,

one point mutation was found in exon 6 at a frequency of 0.006, or 0.6%, and four point mutations

with frequencies from 0.2 to 0.8% in exon 9 (Table 2). However, there is no examples showing that

all inherited mutations for either of these genes were determined.

The unpredictability of the art and the state of the prior art

First, there is the issue of "inherited mutations". As defined by Applicant, such mutations are those that are present in the genome of an individual at conception. However, as pointed out by Thilly (Ann. Rev. Pharmacol. Toxicol., vol. 30, pp. 369-385, 1990; cited in the IDS), the postconcenption somatic mutations can be confused with inherited mutations (page 375, first paragraph). Applicants did not propose how to differentiate between the two classes.

Further, as can be seen by the example of apoE gene (de Knijff, Hum. Mut., vol. 4, pp. 178-194, 1994; see Table 1), for which 44 different mutations were determined prior to 1994, some of them were found only in small numbers of individuals or in particular populations, like German-Caucasian or Japanese. Therefore, even if some of them are present at frequencies above 5×10^{-5} in their respective ethnic populations, they would be undetectable in a general sampling. Taking into account the fact that there are most likely other as yet undiscovered point mutations which may have been inherited, it is unlikely that all inherited point mutations can be determined for any one gene.

The prior art suggests that determination of mutation frequencies and modes of inheritance is not straightforward. Davies et al. (in "Molecular Basis of Inherited Disease", IRL Press, pp. 21-25, 1992; cited in the previous office action), points to the fact that determination of the type and presence of inheritance is not easy. "First, since parents give their children both their genes and their environment, the fact that a character tends to run in a families does not prove that it is genetic-it might, for example, be due to a bad diet. Secondly, most characters depend on interactions between one or more gene loci, conferring susceptibility, and an environmental trigger. Such characters are exceedingly refractory to current methods of genetic analysis; despite their great clinical importance, very little progress has been made in the genetic analysis of schizophrenia, depressive psychosis or other major diseases." (page 20, last paragraph; page 21, first paragraph).

Cavalli-Sforza et al. (in The Genetics of Human Populations, W.H. Freeman and Company, San Francisco, 1971, pp. 71-110; cited in the previous office action), discuss deleterious mutations. They teach that such mutations are subject to selection, which eliminates the mutant genes when their frequency increases (page 72, paragraphs 3 and 4). They estimate equilibrium frequencies of recessive deleterious and dominant deleterious mutations assuming equilibrium between arising new mutations and selection. For a deleterious recessive gene, the gene frequency is estimated as $\sqrt{\mu/s}$, where μ is the mutation rate and s is the selection coefficient (page 79, last paragraph; page 80; page 81, first and second paragraphs). For a lethal gene, s = 1, and if the mutation rate is of the order of 10^{-6}, the frequency of the gene is 0.1%, whereas with a very high mutation rate of 10^{-4}, the gene frequency would reach 1%. Therefore, a lot of inherited point mutations would not be determined because of the absence of individuals carrying them in the population studied.

Finally, reliable estimate of gene frequencies of particular diseases and mutation rates may not be possible because of their presence in isolated populations. De la Chapelle (J. Med. Genet., vol. 30, pp. 857-865, 1993; cited in the previous office action) describes mapping of genes associated with certain diseases in isolated human populations in Finland. In particular, they teach that rare dominantly inherited diseases can be highly enriched in isolated populations if they do not confer selective disadvantage (page 859, third paragraph). The same is true for autosomal recessive mutations (page 861, 6th full paragraph). Therefore, mutation frequencies in isolated populations might be much higher than in general population for the same type of mutation (dominant or recessive).

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant

number of parameters, which would have to be studied to apply this method to determination of

recessive and dominant alleles, which are harmful or interfere with reproduction. At least one study

would need to be performed in the general population by sequencing at least one gene, determining

all of the point mutations in such gene and determining which one of them are hereditary mutations.

Since these mutations should be inherited, additional effort would be required to genotype all of the

individuals' parents and/or siblings, to determine which one of such point mutations are indeed

inherited. Further, since dominant deleterious mutations usually result in removal of the affected

individuals from populations, they may not be detectable at al. Therefore, to detect very rare

mutations, extremely large populations would need to be screened. This would require years of

inventive effort, with each of the many intervening steps, upon effective reduction to practice, not

providing any guarantee of success in the succeeding steps.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the detection of

mutation frequencies depend upon numerous known and unknown parameters such as the

population size, selection, mutation rate, etc., the factor of unpredictability weighs heavily in favor

of undue experimentation. Further, the prior art and the specification provides insufficient guidance

to overcome the art recognized problems in the determination of inherited mutation frequencies of

all point mutations in a given gene. Thus given the broad claims in an art whose nature is identified

as unpredictable, the unpredictability of that art, the large quantity of research required to define

these unpredictable variables, the lack of guidance provided in the specification, the absence of a

working example and the negative teachings in the prior art balanced only against the high skill

level in the art, it is the position of the examiner that it would require undue experimentation for one

of skill in the art to perform the method of the claim as broadly written.

8.   The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9.   Claim 59 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing

to particularly point out and distinctly claim the subject matter which applicant regards as the

invention.

Claim 59 is indefinite over the recitation of "...separately determining the set of all inherited

point mutations occurring at a frequency 5×10^{-5} in members of the same population..." (lines 5, 6).

It is not clear what is meant by "separately determining". Does it mean determining the set in each

individual, or in each age group?

Claim interpretation

10.   A) In claims 23 and 62, since the minimum point mutation number is one and a minimum

number of genes is also one, the sum of the frequencies is identical to a frequency of just one

mutation in one gene.

B) The term "obligatory knock-out point mutation" has been defined by Applicant as point

mutations which necessarily inactivate the gene (page 25, lines 10, 11). However, Applicant did not

define what it means for a gene to be inactive. Therefore, any point mutations within a gene are

considered as obligatory knock-out mutations, since potentially they can change protein activity.

Claim Rejections - 35 USC § 102

11.   The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the

basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12.   Claims 23 and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Kervinen et al.

(Atherosclerosis, vol. 105, pp. 89-95, 1994; cite in the IDS; cited in the previous office action), as

evidenced by Margaglione et al. (Stroke, vol. 29, pp. 399-403, February 1998) and Paik et al.

(PNAS, vol. 82, pp. 3445-3449, 1985).

Regarding claims 23 and 62, Kervinen et al. teach identification of a harmful alleles, the

method comprising:

a) identifying one or more inherited point mutations that are found in one or more genes or

portions thereof of a population of young individuals, determining the frequency with which each

point mutation occurs, and calculating the sum of the frequencies of all point mutations identified

for each gene or segment (Kervinen et al. teach identifying frequencies of apolipoprotein E (apo E)

and apolipoprotein B (apo B) polymorphisms in populations of young adults (Abstract; Fig. 2;

Table 3, 4).);

b) identifying one or more inherited point mutations that are found in one or more genes or

portions thereof of a population of aged individuals, determining the frequency with which each

point mutation occurs, and calculating the sum of the frequencies of all point mutations identified

for each gene or segment (Kervinen et al. teach identifying frequencies of apolipoprotein E (apo E)

and apolipoprotein B (apo B) polymorphisms in populations of nonagenarians (Abstract; Fig. 2;

Table 3, 4).);

c) comparing the sum of the frequencies of point mutations that are found in a selected gene

or portion thereof of the young population calculated in a) with the sum of the frequencies of point

mutation that are found in the same gene or portion thereof of the aged population calculated in b),

wherein a significant decrease in the sum of the frequencies of point mutations in the aged

population indicates that said selected gene carries one or more harmful allele (Kervinen et al. teach

comparing the frequencies of apoE ε4 allele and the EcoRI R- apoB allele between the young adults

and nonagenarians, and finding that frequencies of these two alleles were significantly lower in the

nonagenarins than in young adults (Fig. 2, Table 4; page 92, last paragraph; page 93). Kervinen et

al. conclude that the presence of apoE ε4 allele is a major risk factor for coronary heart disease

(CHD) (page 93, last paragraph), and suggest that the R- allele may be a risk factor for a CHD (page

94, fourth paragraph).

Regarding claim 62, Kervinen et al. do not specifically teach that apoE polymorphisms are

knock-out point mutations (or point mutations which inactivate the gene, according to Applicant's

definition). Margaglione et al. teach that that the apoE ε4 allele results in the amino acid

substitution of Cys -> Arg at position 112. Further, Paik et al. teach that the Cys -> Arg mutation is

caused by a T -> C substitution at position 3745 of the apoE gene (page 3448, second paragraph).

Therefore Kervinen et al. anticipate this limitation of claim 62.

13.   No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner

should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The

examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor,

Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where

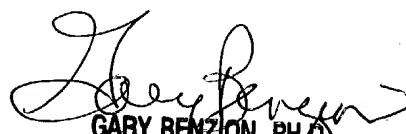this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent

Application Information Retrieval (PAIR) system. Status information for published applications

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applications is available through Private PAIR only. For more information about the PAIR system,

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contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

August 12, 2004

Teresa Strzelecka

Patent Examiner

JEFFREY FREDMAN
PRIMARY EXAMINER

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600